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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/516,405	11/30/2004	Wolfgang Demmer	9013.0099	2828

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EXAMINER	
FERNANDEZ, SUSAN EMILY	
ART UNIT	PAPER NUMBER
1651	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/516,405	DEMMER ET AL.	
	Examiner	Art Unit	
	SUSAN E. FERNANDEZ	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 August 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11,14 and 15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11,14 and 15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The amendment filed August 30, 2010, has been received and entered.

Claims 1-10, 12, 13, and 16 are cancelled. Claims 11, 14, and 15 are pending and examined on the merits.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 11 stands rejected under 35 U.S.C. 103(a) as being unpatentable over Zeng et al. (Ind. Eng. Chem. Res. 1998. 37: 159-165) in view of Langlotz et al. (Journal of Chromatography. 1992. 591: 107-113).

Zeng et al. points out that affinity membrane chromatography brings solute into close proximity to bound ligands through convective transport (page 159, first paragraph). Specifically, Zeng et al. discloses a membrane on which p-aminobenzamidine is immobilized (abstract). It is noted that "p-Aminobenzamidine (PAB) can serve as a ligand for trypsin and trypsin-like enzymes (such as urokinases, plasminogen activators, and serine proteases)" (page 160, first paragraph). A PAB-chitosan affinity membrane is obtained by first cross-linking a chitosan membrane, incorporating carboxyl groups in the cross-linked chitosan membrane by immersing the membrane in a succinic anhydride solution for 16 hours, blocking unreacted amino groups by using an acetic anhydride and methanol solution for 2 hours, removing residual acetic anhydride and succinic anhydride by NaOH immersion for 1 hour, and then coupling the PAB to the treated chitosan membrane (page 160, second column, first paragraph). Ten PAB-chitosan flat membranes were then sandwiched in a cartridge having four inlet ports and one outlet port (page 161, first full paragraph). The protein solution for treatment was loaded into the cartridge with a peristaltic pump (page 161, first full paragraph). Please note the PAB is coupled to the modified chitosan membranes via covalent binding between the amine terminal of PBA and the oxygen molecule of the carboxyl terminal of the succinylated chitosan membrane.

Therefore, Zeng et al. teaches a device for removing proteases from biological and pharmaceutical solutions comprising a housing having a fluid inlet and a fluid outlet, said housing containing a plurality of membranes arranged therein in series, wherein said membranes have PAB (a protease inhibitor, per the instant claims) bound thereto. Zeng et al further teach using said device for adsorption of trypsin (page 164, first two paragraphs) and for purification of trypsin from a crude trypsin solution (page 164, first column, last paragraph through second

column, second paragraph), which reads on a method for removing proteases from a protease-containing fluid. It was concluded that the PAB-chitosan affinity membranes have "...high permeability, good mechanical properties, chemical stability, and high ligand density" (page 165, last paragraph) and can be efficient for trypsin purification (abstract).

Zeng et al. does not expressly disclose that the PAB membranes for trypsin purification consist essentially of epoxy-functionalized microporous membranes each containing epoxy groups chemically coupled to PAB.

Langlotz discloses coupling protein to epoxy-activated membranes (page 107, second column, last paragraph). The studies were performed with Sartobind Epoxy, an epoxy-activated polymeric composite membrane (page 108, first column, third full paragraph) wherein protein solutions were circulated through the membranes for 2-26 hours (page 108, first column, last full paragraph). Proteins that were tested were protein A, rabbit IgG, and soybean trypsin inhibitor (page 108, first column, first full paragraph and page 109, second column) all of which coupled to the epoxy-activated membrane (page 109, second column). Please note that proteins couple to the epoxy-activated membrane via covalent binding between the amine terminal of the protein and the oxygen of the epoxy group.

It is therefore submitted that, at the time the invention was made, it would have been *prima facie* obvious to the person of ordinary skill in the art to have substituted the epoxy-activated membrane of Langlotz et al for the chitosan membrane taught by Zeng et al, and then couple the PAB to the epoxy-activated membrane. One of ordinary skill in the art would have been motivated to do this because it would have required fewer steps and less time in preparing each epoxy-activated-PAB membrane as compared to the chitosan-PAB membranes as taught by

Zeng et al. Specifically, the chitosan membrane must undergo various pretreatment steps prior to coupling the PAB, according to Zeng et al. For pretreatment, the chitosan membrane is cross-linked, the carboxyl groups are incorporated in the cross-linked chitosan membrane by immersing the membrane in a succinic anhydride solution for 16 hours, the unreacted amino groups are blocked by using an acetic anhydride and methanol solution for 2 hours, and then the residual acetic anhydride and succinic anhydride are removed by NaOH immersion for 1 hour (page 160, second column, first paragraph). These pretreatment steps require a total of at least 19 hours. On the other hand, for binding a protein to the epoxy-activated membrane of Langlotz et al., the Sartobind Epoxy membrane does not need to be pretreated.

Furthermore, one of ordinary skill in the art would have been motivated to have made the substitution since Langlotz et al. recognizes that affinity membranes, such as a p-benzamidine membrane, can be used for removal of the proteases thrombin and kallikrein from blood (page 107, second column, first paragraph). One would have had a reasonable expectation of successfully coupling PAB to the activated epoxy membranes of Langlotz et al because, like the proteins taught by Langlotz et al, PAB reacts via a terminal amine group, and thus is chemically able to covalently bind to the epoxy membrane via the oxygen of the epoxy group. Therefore, though PAB is not a protein, per se, it is capable of binding to epoxy groups in the same manner as proteins. Thus, claim 11 is rendered obvious.

A holding of obviousness is clearly required.

Claims 11, 14, and 15 stand rejected* under 35 U.S.C. 103(a) as being unpatentable over Hermanson et al. (Immobilized Affinity Ligand Techniques. 1992. Academic Press, Inc. San

Diego, California) in view of Zeng et al, Langlotz et al., and Preece et al. (Journal of Biological Chemistry. 1996. 271(20): 11634-11640).

*The previous Office action erroneously cited claims 1 and 10 in the rejection heading, however, the rejection was clearly directed to the subject matter of claims 11, 14 and 15 (See Page 8, last paragraph, of previous office action, where claims 11, 14 and 15 were specifically cited), Applicants understanding of the typographical error in the Response of 8/30/2010 is appreciated.

Hermanson et al. discloses that "for many biological studies it is essential to completely remove undesirable proteases from biological solutions" (page 355, last paragraph). Examples of affinity supports successfully used for this purpose include immobilized soybean trypsin inhibitor and immobilized p-aminobenzamidine (page 355, last paragraph). The use of immobilized p-aminobenzamidine for protease removal (page 359, second-to-last paragraph) is by column chromatography (pages 318 and 319) as is the use of immobilized soybean trypsin inhibitor (pages 358 and 359).

Hermanson et al. does not expressly disclose that p-aminobenzamidine is immobilized on epoxy-functionalized microporous membranes containing epoxy groups chemically coupled to at least one protease inhibitor selected from the group consisting of p-aminobenzamidine, pepstatin, bestatin, diprotin, antipain, chymostatin, leupetin (leupeptin), E64, and TLCK, wherein the membranes, each containing two different protease inhibitors, are arranged in series in a device comprising a housing having a fluid inlet and a fluid outlet.

Zeng et al. points out that, compared to column chromatography, affinity membrane chromatography bring solute into close proximity to bound ligands through convective transport

(page 159, first paragraph). Examples of biospecific ligands incorporated in micro- or macroporous membranes include trypsin inhibitors (page 159, first paragraph). Specifically, Zeng et al. discloses a membrane on which p-aminobenzamidine is immobilized (abstract). A PAB-chitosan affinity membrane is obtained by first cross-linking a chitosan membrane, incorporating carboxyl groups in the cross-linked chitosan membrane by immersing the membrane in a succinic anhydride solution for 16 hours, blocking unreacted amino groups by using an acetic anhydride and methanol solution for 2 hours, removing residual acetic anhydride and succinic anhydride by NaOH immersion for 1 hour, and then coupling the PAB to the treated chitosan membrane (page 160, second column, first paragraph). Ten PAB-chitosan flat membranes were sandwiched in a cartridge having four inlet ports and one outlet port (page 161, first full paragraph). The protein solution for treatment was loaded into the cartridge with a peristaltic pump (page 161, first full paragraph). Therefore, Zeng et al. teaches a device for removing proteases from biological and pharmaceutical solutions comprising a housing having a fluid inlet and a fluid outlet, said housing containing a plurality of membranes arranged therein in series. Zeng et al. demonstrated that the device is efficient for trypsin purification (abstract).

Langlotz et al. discloses coupling protein to epoxy-activated membranes (page 107, second column, last paragraph). The studies were performed with Sartobind Epoxy, an epoxy-activated polymeric composite membrane (page 108, first column, third full paragraph) wherein protein solutions were circulated through the membranes for 2-26 hours (page 108, first column, last full paragraph). Proteins that were tested were protein A, rabbit IgG, and soybean trypsin inhibitor (page 108, first column, first full paragraph and page 109, second column) all of which coupled to the epoxy-activated membrane (page 109, second column).

Substitution of the epoxy activated membranes of Langlotz et all for the chitosan membrane of Zeng et al has been discussed above.

Preece et al. discloses that pepstatin, bestatin, diprotin, antipain, chymostatin, leupetin (leupeptin), E64, and TLCK are serine protease inhibitors (page 11635, second column, first paragraph and page 11637, first column, first full paragraph).

At the time the invention was made, it would have been obvious to the person of ordinary skill in the art to have removed proteases from fluids with the device of Zeng et al. wherein instead of PAB-chitosan flat membranes, the device comprises epoxy-activated membranes each comprising two different protease inhibitors selected from p-aminobenzamidine, pepstatin, bestatin, diprotin, antipain, chymostatin, leupetin (leupeptin), E64, and TLCK. One of ordinary skill in the art would have been motivated to do this since, compared to column chromatography, affinity membrane chromatography bring solute into close proximity to bound ligands through convective transport. Moreover, Zeng et al. demonstrates that a membrane comprising immobilized p-aminobenzamidine is suitable for binding to trypsin. It would have been advantageous to have bound the protease inhibitors to the epoxy-activated membranes of Langlotz et al. rather than the membrane of Zeng et al. as fewer steps and less time would have been required in binding the protease inhibitors to the membranes. There would have been reasonable expectation of success in immobilizing at least one of the protease inhibitors listed above since the epoxy-activated membrane of Langlotz et al. is shown to be suitable for binding molecules via an amine terminal group (such as is found on PAB). Moreover, there would have been a reasonable expectation of success in removing proteases with any of the protease

inhibitors listed as two immobilized protease inhibitors (p-aminobenzamidine and soybean trypsin inhibitor) are suitable for removal of proteases (Hermanson).

Finally, it would have been obvious to have bound two or more different protease inhibitors to the epoxy-activated membrane since it would have reduced the concentration of a variety of proteases in a biological solution.

Given that the membrane is epoxy-activated and is the same membrane used in the claimed invention (Sartobind Epoxy, page 5, lines 16-17), the epoxy groups on the membrane are indeed chemically coupled by a chemical bond to the protease inhibitor(s). Thus, claims 11, 14, and 15 are rendered obvious.

A holding of obviousness is clearly required.

Response to Arguments

Applicant's arguments filed August 30, 2010, have been fully considered but they are not persuasive.

Applicants have traversed the rejection over Zeng et al in view of Langlotz et al on the grounds that the premise of the rejection was that PAB was assumed to be a protein and thus could be coupled to the epoxy-activated membrane of Langlotz et al, yet Applicants assert PAB is not a protein but a low molecular weight compound.

In response, it is submitted that though PAB is not a protein, per se, PAB still contains a terminal amine group and binds to membranes via interaction between the terminal amine and an oxygen molecule on the membrane structure, and thus, like proteins, PAB is capable of binding to the oxygen species in the epoxy group on the membrane. Therefore one would still have had a

reasonable expectation of successfully binding the PAB to the epoxy membrane of Langlotz et al and substituting said membrane into the device of Zeng et al. .

Applicants have traversed the rejection over Hermnason in view of Zeng, Langlotz and Preece on the grounds that Hermanson teaches away from the claimed invention since Hermanson indicates that the best way to immobilize PAB is by using a "spacer arm" to extend PAB "some distance from the matrix."

In response, it is submitted that MPEP 2145, Section X, Part 1, indicate that "'the prior art's mere disclosure of more than one alternative does not constitute a teaching away from any of these alternatives because such disclosure does not criticize, discredit, or otherwise discourage the solution claimed…'" Therefore, rejections over Hermanson must be maintained.

No claims are allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SUSAN E. FERNANDEZ whose telephone number is (571)272-3444. The examiner can normally be reached on Mon-Fri 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mike Wityshyn can be reached on (571) 272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Allison M. Ford/
Primary Examiner, Art Unit 1651

Susan E. Fernandez
Examiner
Art Unit 1651

sef